AD_________________

Award Number: W81XWH-08-1-0273

TITLE: Regularized Reconstruction of Dynamic Contrast-Enhanced MR Images for Evaluation of Breast Lesions

PRINCIPAL INVESTIGATOR: Kimberly A. Khalsa

CONTRACTING ORGANIZATION: The University of Michigan
Ann Arbor, MI 48109-1274

REPORT DATE: September 2009

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE *(DD-MM-YYYY)*
01-09-2009

2. REPORT TYPE
Annual Summary

3. DATES COVERED *(From - To)*
1 Sep 2008 – 31 Aug 2009

4. TITLE AND SUBTITLE
Regularized Reconstruction of Dynamic Contrast-Enhanced MR Images for Evaluation of Breast Lesions

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-08-1-0273

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Kimberly A. Khalsa
Jeffery A. Fessler

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
The University of Michigan
Ann Arbor, MI 48109

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research
and Materiel Command
Fort Detrick, MD 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited.

13. SUPPLEMENTARY NOTES

14. ABSTRACT

The overall goal of this project is to develop, implement, and evaluate methods for improving image quality in dynamic MR imaging. We focus specifically on dynamic contrast-enhanced (DCE) imaging of breast cancer patients. We explore reconstruction methods that use explicit temporal models in object space. Simulation and phantom studies have indicated that our algorithms produce quality reconstructed image sequences that exhibit both high spatial and high temporal resolution.

15. SUBJECT TERMS
Image reconstruction, dynamic contrast-enhanced MRI, breast MRI

16. SECURITY CLASSIFICATION OF: a. REPORT	b. ABSTRACT	c. THIS PAGE	17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
U	U	U	UU	15	USAMRMC
					19b. TELEPHONE NUMBER *(include area code)*

Standard Form 298 (Rev. 8-98)
Prescribed by ANSI Std. Z39.18

Contents

1 Introduction

The overall goal of this project is to develop, implement, and evaluate methods for improving image quality in dynamic magnetic resonance imaging. We focus specifically on dynamic contrast-enhanced (DCE) imaging of breast cancer patients. The fundamental challenge in dynamic MRI is the tradeoff between spatial resolution and temporal resolution. In addressing this problem, most traditional dynamic acquisition methods and associated reconstruction methods have been based on operations in the data domain, known as k-space, implicitly assuming that the object varies smoothly in time. We explore reconstruction methods that instead use explicit temporal models in object space. We develop iterative methods for fitting these models to the measured k-space data using regularized estimators without attempting to synthesize any of the 'missing' k-space data. We hypothesize that DCE-MRI quality can be improved using our proposed reconstruction scheme which includes explicit temporal regularization in object space.

2 Body

2.1 Reconstruction Model and Cost Function Design

Our proposed method for reconstructing DCE MR images is based on minimizing a three term image domain cost function. We call our method Temporal Regularization Use in Image Reconstruction (TRUIR). The first term in the cost function is a data fidelity term, which ensures that the image estimate is consistent with the measured data. The second and third terms in the cost function are weighted spatial and temporal penalty terms. We use these terms to incorporate our *a priori* knowledge about the object, namely that there is a certain smoothness expected in both space and time. The spatial regularizer penalizes large differences between neighboring pixels in space and the temporal regularizer penalizes large differences between neighboring pixels in time. There are regularization parameters α and β that determine the relative weighting within the cost function of the spatial and temporal regularization terms, respectively.

2.2 Simulation Results

As a first validation step, we performed simulations using a digital phantom for which we generated undersampled MR (k-space) data. We subsequently estimated a reconstructed image sequence using our TRUIR method as well as some existing reconstruction methods, including the Keyhole method and Reduced-encoding Imaging by Generalized-series Reconstruction (RIGR) [1–4]. The digital phantom was comprised of a real, bilateral breast image with an inserted (simulated) circular lesion. Because we used a digital phantom, we can compare the spatial resolution and temporal resolution of our reconstructed image sequences to the known true image sequence.

The true enhancement curve, which reflects temporal resolution for the true object, along

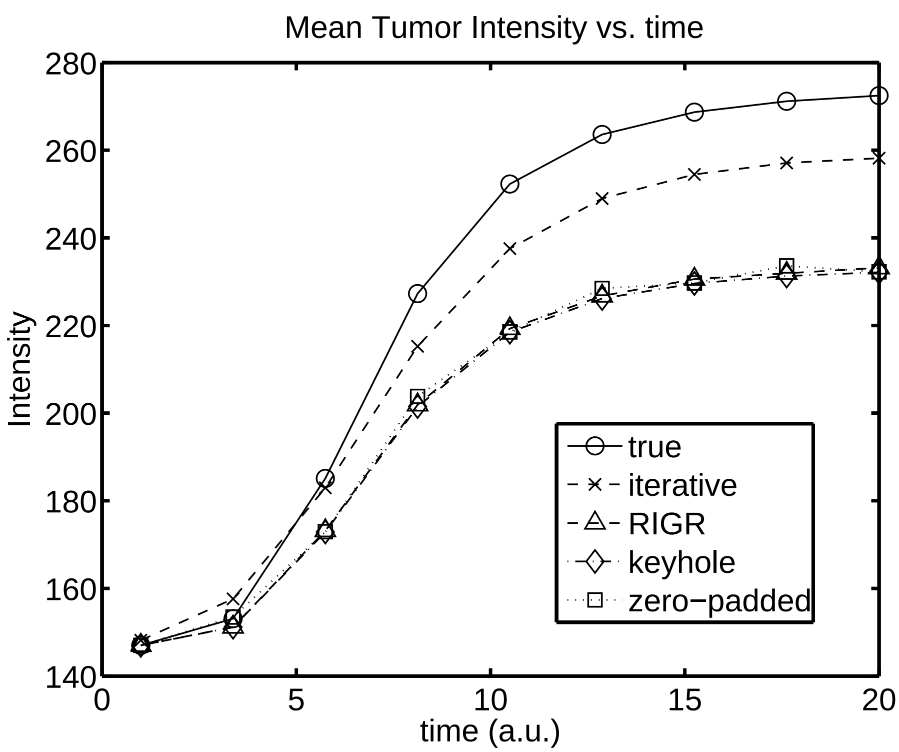

Figure 1: Enhancement curve used in simulations. True curve (solid) and reconstructions.

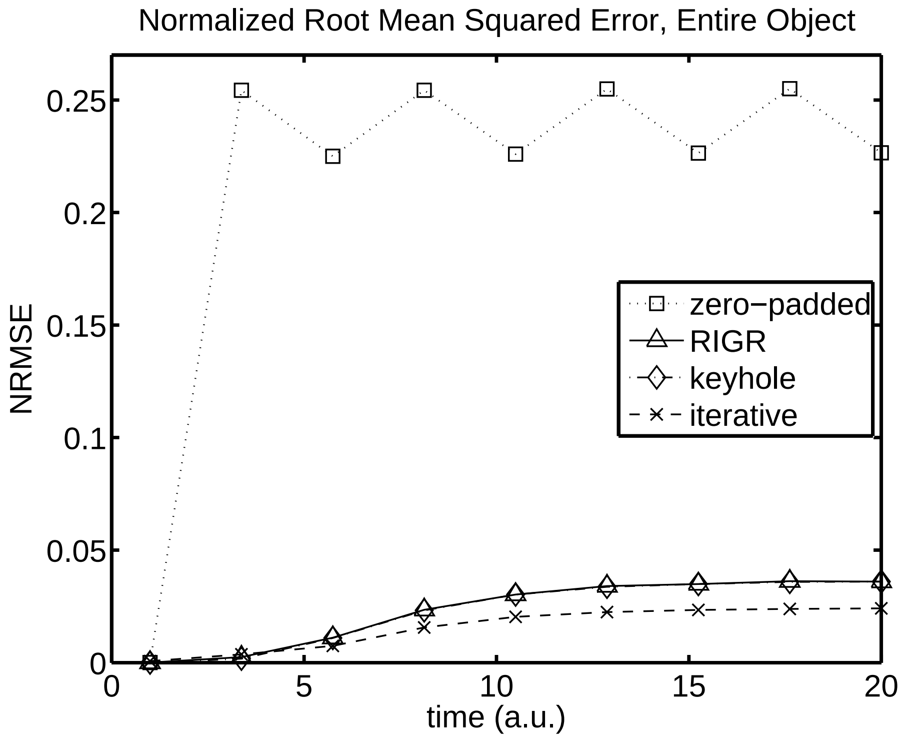

Figure 2: Reconstruction error, entire object.

with enhancement curves from various reconstructions are shown in Fig. 1. The TRUIR reconstruction achieves an enhancement curve much closer to the true enhancement curve than the other methods.

As a quantitative measure, we computed the normalized root mean square error (NRMSE) for each frame of the reconstructed sequences over the entire image, as well as within a region of interest (ROI) surrounding the lesion. The error over the object at each frame is shown in Fig. 2. The error of the zero-padded reconstruction is huge, as expected, due to the severe undersampling of the dynamic frames. The error in the Keyhole and RIGR methods is significantly smaller, although both are outperformed by our iterative, TRUIR reconstruction.

Because accurate reconstruction of morphological features is a primary goal of our method, defining a ROI to surround the lesion allows us to potentially capture poor reconstruction of the lesion edges/margins. The NRMSE within this ROI is shown in Fig. 3 across time. Again, our iterative TRUIR method has lower error than the other reconstructions.

The reason TRUIR has lower error than the competitors can be seen by examining the images reconstructed for the 5-th time frame in Fig. 4. From left to right, top to bottom, the images are: true image, zero-padded reconstruction, Keyhole reconstruction, RIGR reconstruction, and our TRUIR reconstruction. The effect of undersampling is best seen in the zero-padded reconstruction, which shows significant blur in the undersampled direction. While both Keyhole and RIGR produce sharper reconstructions than zero-padding, the dynamic feature, the lesion, still shows significant blur in the undersampled direction. Because

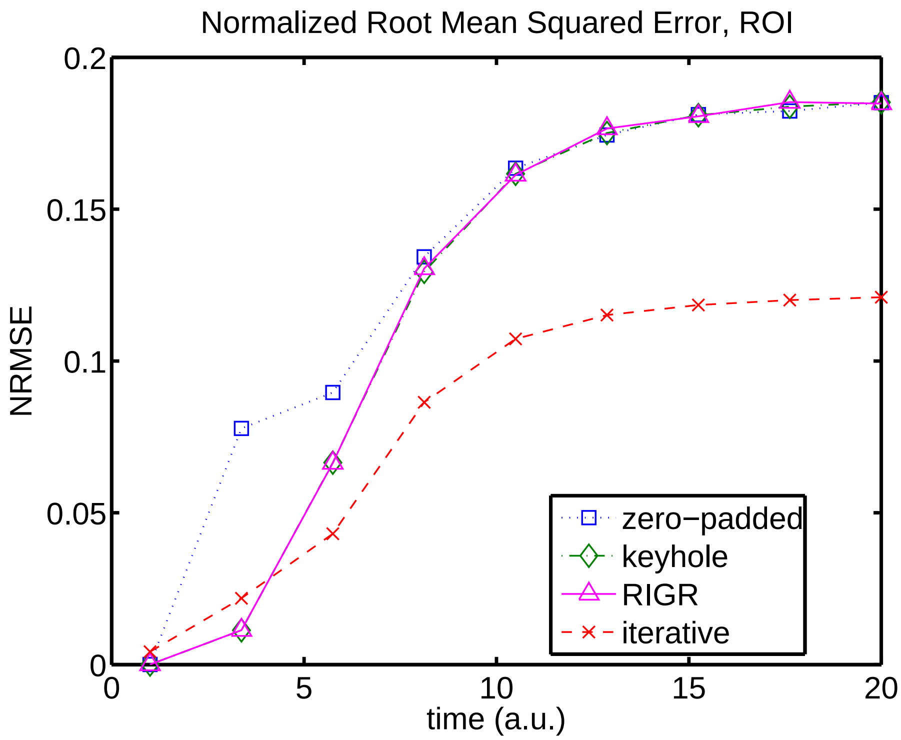

Figure 3: Reconstruction error in ROI surrounding lesion.

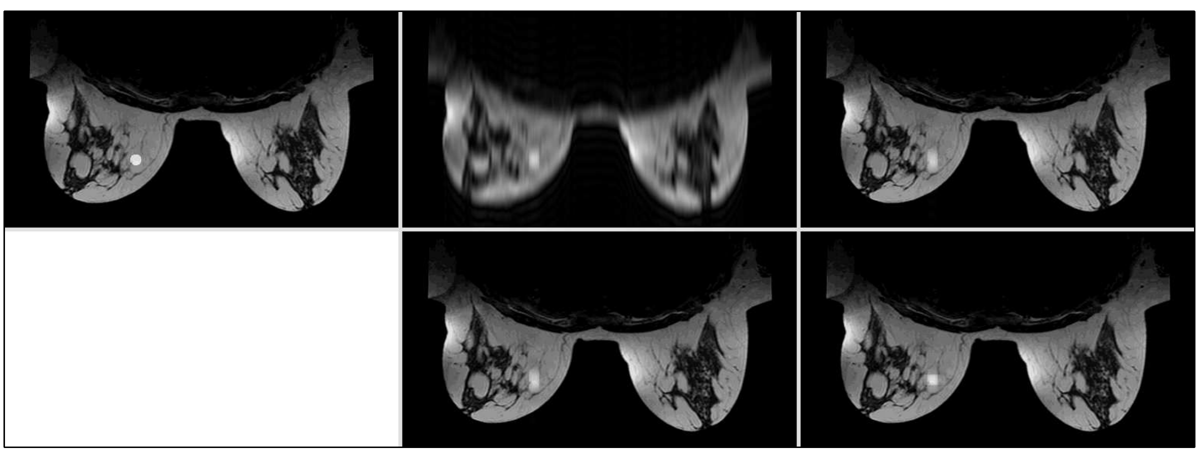

Figure 4: 5th frame of reconstructed image sequence. Top row (left to right): True image, zero-padded reconstruction, Keyhole reconstruction. Bottom row (left to right): RIGR reconstruction, our TRUIR reconstruction.

our TRUIR method jointly estimates the entire image sequence at once, it is better able to take advantage of the all of the measurements at hand to produce an image sequence with significantly reduced blur of the dynamic feature.

2.3 Algorithm Acceleration

A drawback of iterative reconstruction methods, compared to conventional methods, is increased computation time. For our proposed method, the most computationally expensive step in determining the image estimate is computing the gradient of the cost function. We were able to accelerate our computation by exploiting Toeplitz matrices in this step [5]. This acceleration technique has previously been investigated for use in static, field-corrected MR image reconstruction [6], but, to our knowledge, we are the first to apply it to dynamic MRI. For this study, the Toeplitz-modified algorithm was 1.7 times faster than the original algorithm.

2.4 Extension to Parallel Imaging

In the past decade the idea of simultaneously using multiple receiver coils to acquire MR data has been introduced and the practice is now widespread [7, 8]. This is known as *parallel imaging* and, in general, reduces the required scan time. Therefore we deemed it important to incorporate parallel imaging into our methods and have done so.

2.5 Phantom Results

For an initial phantom study, we acquired data from an in-house dynamic breast phantom using a 3T Philips scanner and a 7-coil breast array. The phantom includes tubes through which contrast agent flowed during the scan.

We reconstructed this 7-frame dynamic data using two techniques, 1) a traditional frame-by-frame approach which utilizes homodyning [9] and sensitivity encoding (SENSE) [8], and 2) our TRUIR reconstruction. Fig. 5 shows a slice of the reconstructions from frame 4 for both the frame-by-frame approach (top) and TRUIR (bottom). The frame-by-frame reconstruction shows rippling artifact around the dynamic features, which can be better seen in the enlargment in Fig. 6. These artifacts are somewhat reduced in the TRUIR reconstruction.

Fig. 7 shows the enhancement curves for a dynamic region of the phantom. Both methods show similar temporal characteristics. Fig. (8 shows the entire dynamic image sequence reconstructed using TRUIR. Only the left half of the phantom is shown since the right half had no dynamic activity. This sequence illustrates the overall spatio-temporal resolution of the TRUIR reconstruction.

2.6 Choice of Regularization Parameters

A challenging aspect of any regularized formulation is choosing appropriate regularization terms, as well as determining the relative weights of these terms. In our formulation, the

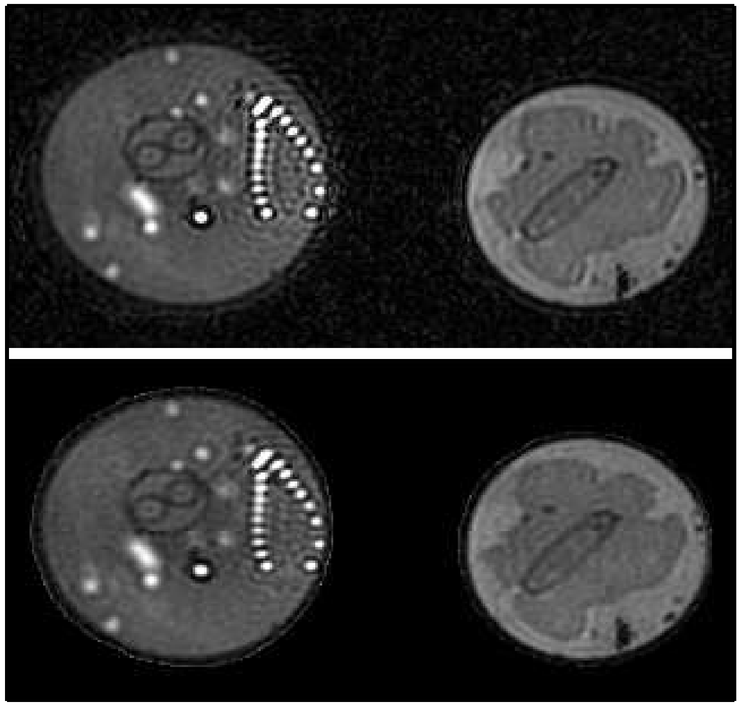

Figure 5: Reconstructions of frame 4: frame-by-frame (top), and TRUIR (bottom).

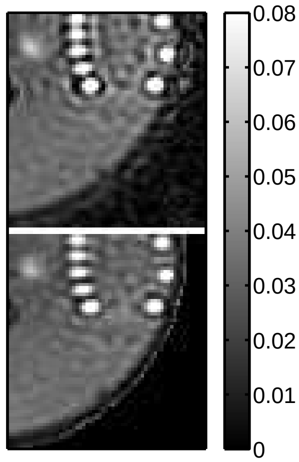

Figure 6: Enlargled section of reconstructions from Fig. (5). Frame-by-frame (top) and TRUIR (bottom).

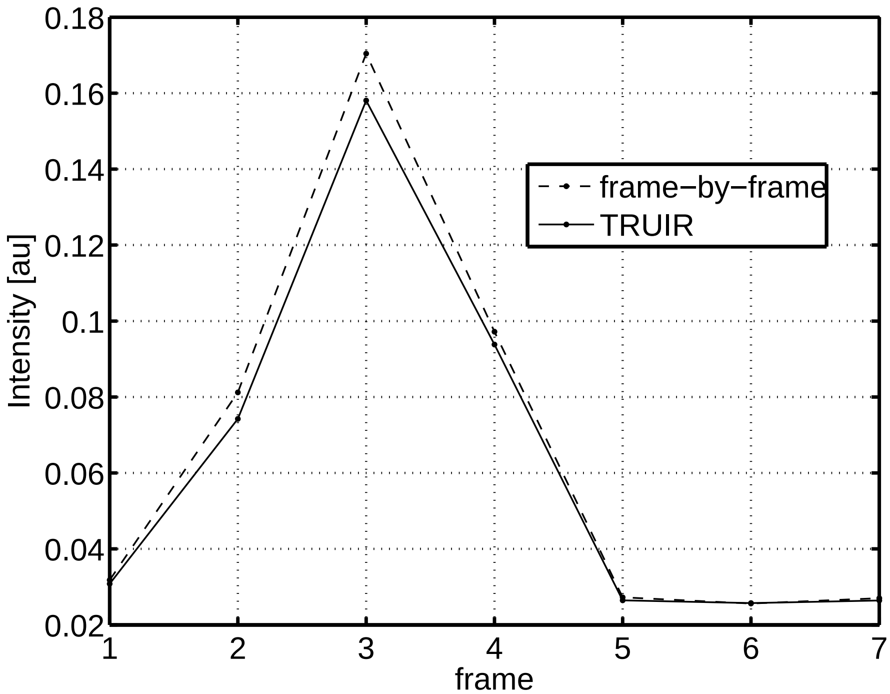

Figure 7: Enhancement curve for dynamic phantom.

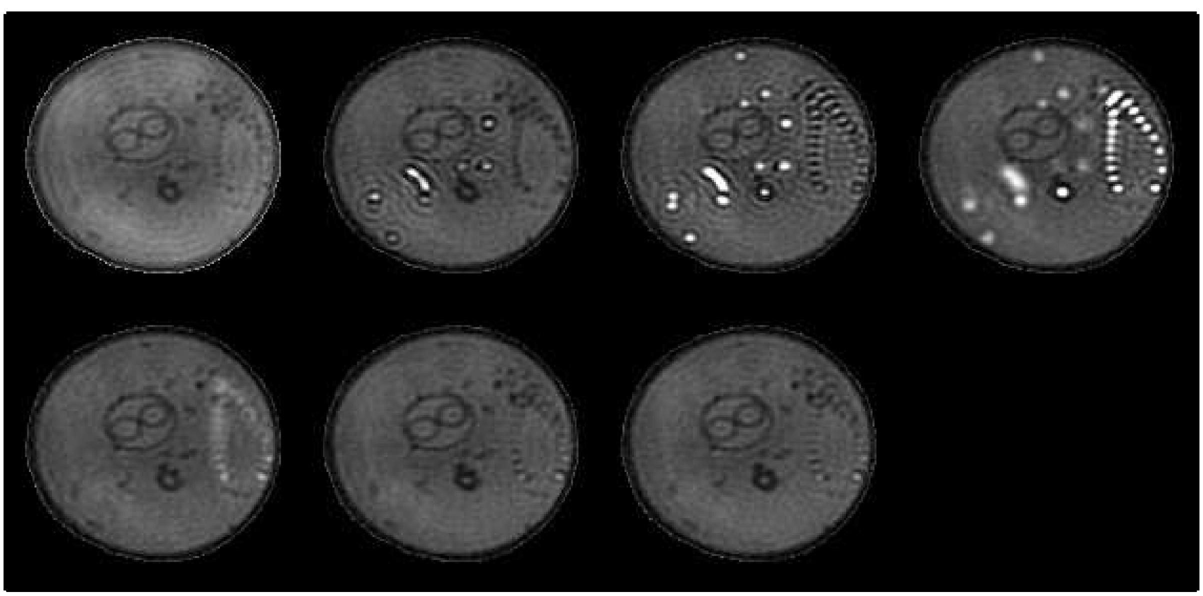

Figure 8: TRUIR reconstruction of 7 frames of a dynamic breast phantom (left half only).

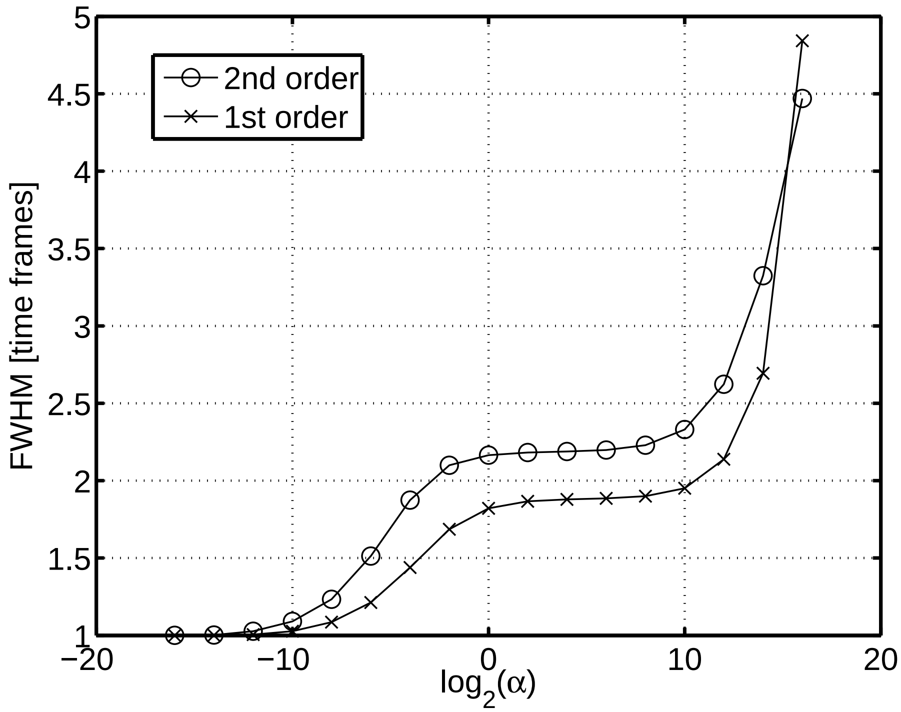

Figure 9: FWHM of temporal PSF for TRUIR as a function of temporal regularization parameter α.

weighting of these terms is implemented with temporal and spatial regularization parameters, α and β. Regularization parameter choice can significantly influence the quality of the reconstructed images. For practical use of our reconstruction approach, one must understand how the regularization parameters α and β in the cost function affect the reconstructed images.

We've aimed to address the issue of regularization parameter choice by analyzing the resolution properties of the TRUIR method. To do this, we examined the local impulse response in space and time. Similar analysis of penalized-likelihood reconstruction for (static) tomography was presented in [10].

Fig. 9 shows the effect of the temporal regularization parameter α on the Full Width at Half Maximum (FWHM) of the Point Spread Function (PSF) in time.

To gain a better understanding of how parameter choice affects dynamic images, we performed a simulation of contrast agent uptake using a real bilateral breast image with an inserted (simulated) circular lesion. The lesion exhibited enhancement over time according to the curve in Fig. 10, while the rest of the image remained static.

We reconstructed the data using $\beta = 2^4$ and first order temporal regularization with several values of the temporal regularization parameter α, which weights the temporal penalty term in our reconstruction formulation. Fig. 11 shows the reconstructed images from the 5th time frame; zero-padded reconstruction and Keyhole reconstruction are shown for reference. The "tumor" enhancement curves from the reconstructed images appear in Fig. 10.

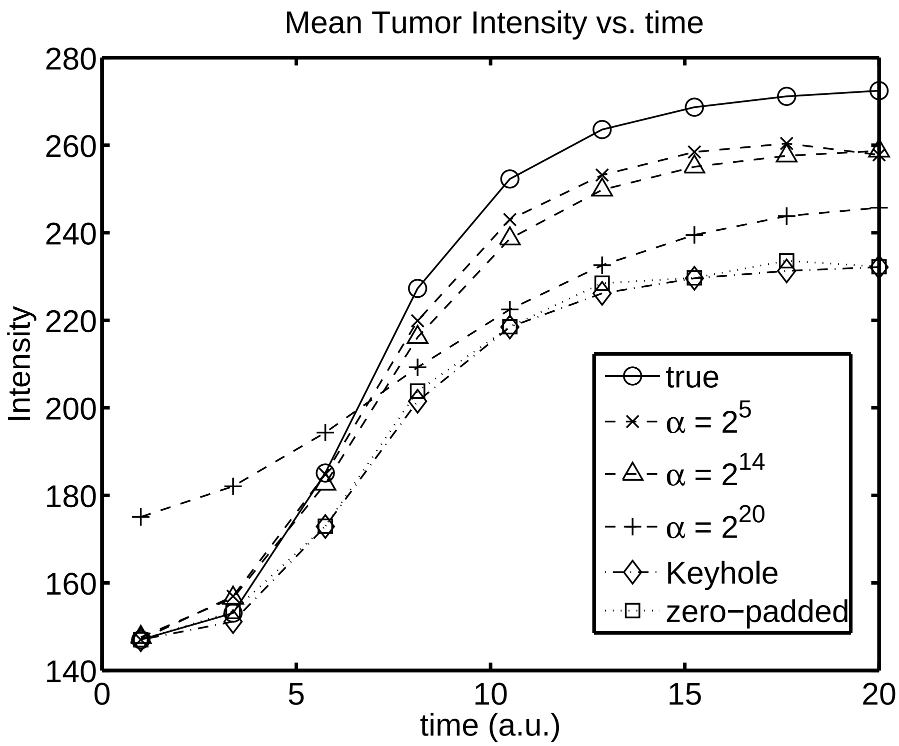

Figure 10: Enhancent curve for simulated lesion and reconstructions

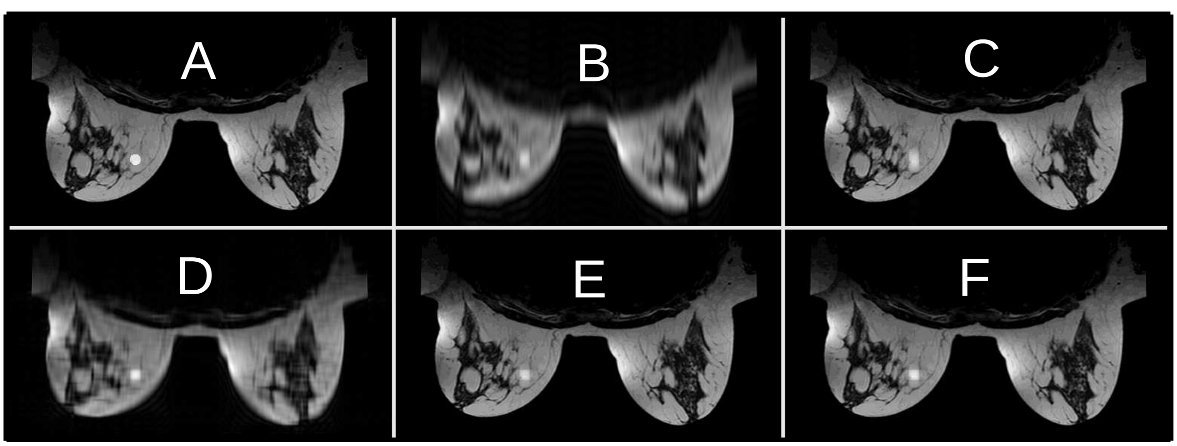

Figure 11: 5th frame of true image (A) and reconstructions with zero-padding (B), Keyhole (C), TRUIR with $\alpha = 2^5$ (D), TRUIR with $\alpha = 2^{20}$ (E), TRUIR with $\alpha = 2^{14}$ (F).

Using an α that is too large degrades the temporal dynamics of the reconstructed sequence, as can be seen for $\alpha = 2^{20}$ in Fig. 10. However, for this value of α the reconstructed image from the middle frame of the dynamic sequence, shown in Fig. 11(E), has good spatial resolution. In this case the large weighting of the temporal regularization term in the cost function enforces strong correlation between frames. The result is a sequence of reconstructed images with excellent spatial resolution, but flattened enhancement curve, i.e., poor temporal resolution.

Choosing α too small can also degrade the quality of the reconstructed images. Fig. 11(D) shows a reconstructed image using $\alpha = 2^5$. This image appears quite blurry because the temporal regularization term is not large enough to overcome the spatial blur (due to under-sampling of the data in the individual frames). Note that the corresponding enhancement curve for $\alpha = 2^5$ in Fig. 10 shows good temporal resolution.

In summary, we need α large enough to provide adequate "connectivity" between the frames, but small enough so that the reconstructed image sequence correctly reflects dynamic changes in the object. In this simulation, $\alpha = 2^{14}$ provided such a balance. The reconstructed enhancement curve in Fig. 10 for $\alpha = 2^{14}$ is a good fit to the true enhancement curve, and the reconstructed image in Fig. 11(F) has good spatial resolution.

2.7 Deviations from Original Statement of Work

Due to time constraints, we no longer plan to generalize our algorithms to incorporate motion correction during this project period, as outlined in the original Statement of Work.

3 Key Research Accomplishments

- Developed and implemented dynamic MR image reconstruction algorithms that are based on explicit temporal models in object space.
- Extended the algorithms to incorporate parallel imaging techniques.
- Evaluated algorithms using simulation and phantom studies, with promising results.
- Algorithm acceleration. Decreased computation time by exploiting Toeplitz matrices in our reconstruction.
- Investigated choice of algorithms' regularization parameters based on desired spatial and temporal resolution.

4 Reportable Outcomes

- Applied for and awarded NIH grant 1P01 CA87634-06A2, Project 3: Image reconstruction methods for dynamic contrast-enhanced (DCE) MRI of breast cancer.
- PI successfully completed the qualifying examination and achieved candidacy during this grant period.

5 Conclusion

Dynamic constrast-enhanced MRI studies demand both high spatial and high temporal resolution. We want high spatial resolution to visualize morphology and we want high temporal resolution to accurately follow the tracer kinetics of the tissue.

We have developed a reconstruction scheme based on an image domain model that does not attempt any data domain recovery, but rather explicitly uses the assumption of temporal smoothness in the image domain to estimate the image sequence that best fits the available data. We extended our methods to incorporate parallel imaging and have evaluated the developed methods using both simulations and phantom studies, which both gave promising results. We also investigated a resolution-based approach to choosing the regularization parameters required by our algorithms, and implemented some acceleration schemes to decrease the computation time required for our algorithms.

In the coming year, we will explore a variety of 2D k-space sampling trajectories to determine which may provide better spatiotemporal resolution. We will also use our algorithms to reconstruct MR data from breast cancer patients undergoing neoadjuvant (pre-surgical) chemotherapy. We will examine the potential of kinetic parameters computed from our images to serve as early predictors for tumor response to chemotherapy and will evaluate the quality of our reconstructed images compared to those currently used in the clinic.

References

[1] J. J. Van Vaals, M. E. Brummer, W. T. Dixon, H. H. Tuithof, H. Engels, R. C. Nelson, B. M. Gerety, J. L. Chezmar, and J. A. Den Boer, "Keyhole method of accelerating imaging of contrast agent uptake," *J. Mag. Res. Im.*, vol. 3, no. 4, pp. 671–5, July 1993.

[2] Z-P. Liang and P. C. Lauterbur, "An efficient method for dynamic magnetic resonance imaging," *IEEE Trans. Med. Imag.*, vol. 13, no. 4, pp. 677–86, Dec. 1994.

[3] J. M. Hanson, Z-P. Liang, E. C. Wiener, and P. C. Lauterbur, "Fast dynamic imaging using two reference images," *Mag. Res. Med.*, vol. 36, no. 1, pp. 172–5, July 1996.

[4] Z-P. Liang, B. Madore, G. H. Glover, and N. J. Pelc, "Fast algorithms for GS-model-based image reconstruction in data-sharing Fourier imaging," *IEEE Trans. Med. Imag.*, vol. 22, no. 8, pp. 1026–30, Aug. 2003.

[5] R. H. Chan and M. K. Ng, "Conjugate gradient methods for Toeplitz systems," *SIAM Review*, vol. 38, no. 3, pp. 427–82, Sept. 1996.

[6] J. A. Fessler, S. Lee, V. T. Olafsson, H. R. Shi, and D. C. Noll, "Toeplitz-based iterative image reconstruction for MRI with correction for magnetic field inhomogeneity," *IEEE Trans. Sig. Proc.*, vol. 53, no. 9, pp. 3393–402, Sept. 2005.

[7] D. K. Sodickson and W. J. Manning, "Simultaneous acquisition of spatial harmonics (SMASH): Fast imaging with radiofrequency coil arrays," *Mag. Res. Med.*, vol. 38, no. 4, pp. 591–603, Oct. 1997.

[8] K. P. Pruessmann, M. Weiger, M. B. Scheidegger, and P. Boesiger, "SENSE: sensitivity encoding for fast MRI," *Mag. Res. Med.*, vol. 42, no. 5, pp. 952–62, Nov. 1999.

[9] D. C. Noll, D. G. Nishimura, and A. Macovski, "Homodyne detection in magnetic resonance imaging," *IEEE Trans. Med. Imag.*, vol. 10, no. 2, pp. 154–63, June 1991.

[10] J. A. Fessler and W. L. Rogers, "Spatial resolution properties of penalized-likelihood image reconstruction methods: Space-invariant tomographs," *IEEE Trans. Im. Proc.*, vol. 5, no. 9, pp. 1346–58, Sept. 1996.